Remarks

Claims 40-96 are pending and stand rejected in the Office Action prior to this amendment and response. The Examiner is requested to reconsider the application in view of the instant amendments and remarks and to find the claims allowable.

Claims 40 and 54 are amended to add the term "subsequently" between step i) and step ii) of part b) to emphasize that the steps are carried out separately. Claims 47-49, 60-62 and 90-92 are amended to add the term "which is covalently coupled" after the term "thermally labile radical initiator" to emphasize the fact that the thermally labile radical initiator is covalently linked to an amino nitrogen. These points are clear from the description, especially the Examples, as well as the claims prior to amendment. Claims 67-69 are amended as discussed below. It is believed that no new subject matter is added by any amendment.

Claim Rejections under 35 U.S.C. § 112

Claims 67-69 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is noted that the use claims are lacking active, positive steps. To obviate this basis for rejection, claims 67 and 68 are amended to method of using claims based on the description at, inter alia, page 4, paragraph beginning at line 5, the Examples and the Drawings, to provide steps to support the use. Claim 69 is amended to be an article of manufacture claim referring to claim 40. Accordingly, the Examiner is requested to remove the claim rejections under 35 U.S.C. § 112, second paragraph.

Claim Rejections under 35 U.S.C. § 101

Claims 67-69 stand rejected under 35 U.S.C. § 101 as being unpatentable because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. As noted above, to obviate this basis for rejection, claims 67 and 68 are amended to method of using claims based on the description at, inter alia, page 4, paragraph beginning at line 5, the Examples and the Drawings, to provide steps to support the

use. Claim 69 is amended to be an article of manufacture claim dependent from claim 40. Accordingly, the Examiner is requested to remove the claim rejections under 35 U.S.C. § 101.

Claim Rejections Under 35 U.S.C. § 103

At point 8 of the Office Action, claims 40-66, 80-82, 84-86 and 89-96 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,556,708 to Horl et al. (hereinafter "Horl") in view of U.S. Patent No. 5,037,656 to Pitt et al. (hereinafter "Pitt") and evidenced by Drumheller in "Surface Immobilization of Adhesion Ligands for Investigations of Cell-Substrate Interactions" (hereinafter "Drumheller"). This basis for rejection is respectfully traversed as discussed below. The Examiner notes regarding the method limitations recited in at least claim(s) 40-53 that, even though a product-by-process is defined by the steps by which the product is made, determination of patentability is based on the product itself and that if the product-by-process is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.

As a first point, Applicants point out that there is no reason to combine Pitt Drumheller with respect to Horl in relation to the instant invention. As a second point, Applicants submit that, even if the teachings of the cited references are combined, the Examiner has not met the burden of establishing prima facie obviousness as to the instant claims. Further, even if it is considered that prima facie obviousness has been shown, the obviousness is rebutted.

Horl "relates to a process for the grafting of nitrogen-containing polymers, to whose nitrogen atoms substitutable hydrogens are linked, with ethylenically unsaturated monomers as well as to the graft copolymerizates obtained in this process." Col. 1, lines 8-12. Horl discloses a 'one-pot' process "for grafting nitrogen-containing polymers, to whose nitrogen atoms substitutable hydrogen atoms are linked, with ethylenically unsaturated monomers in such a manner that the monomers are reacted with the polymers in the presence of a water-containing medium, carbon tetrachloride and of a reducing agent." Col. 4, paragraph beginning at line 25. Thus, Horl discloses the use of a redox reaction based on reducing agents for starting the reaction. The preferred reducing agent is said to be sodium dithionite which is applied at a redox potential of especially between -200 and -300 mV.

Pitt does not relate to "a structure comprising adjacent functional polymer chains on the substrate surface" having the structure of the product of the instant invention.

Pitt "relates to a microporous or ultrafiltration membrane containing a cell growth promoting substance...formed from a porous membrane substrate." Col. 1, lines 17-19. Although Pitt mentions "a hydrophilic composite porous membrane comprising a porous substrate having a permanent coating grafted and/or deposited thereon..." (Col. 2, lines 34-36), the teaching of Pitt is directed to processes and products in which "the coating polymer is directly coated onto the porous substrate without the utilization of an intermediate binding chemical moiety." Col. 2, lines 46-48. "The cell attachment and growth promoting composition is entrained in the coating..." Col. 2, lines 51-53. Thus, any grafting onto the named substrates, polyamides (Nylon), polytetrafluoroethylene, polycarbonate, polyvinylidene fluoride, polysulfones, polyethersulfones (Col. 3, lines 14-19) must occur as part of the radical polymerization reaction under circumstances in which a grafting process can occur.

The grafting process in such a situation is summarized in Horl beginning at Col. 1, line 15. It will be clear that in such a grafting process the grafting involves the formation of a radical on the substrate and does not take place at any sharply defined position of the base polymer. Horl at Col. 1, lines 65-67.

In the Office Action at page 5, it is asserted that Pitt discloses: "Covalently coupling a thermally labile radical initiator to the membrane (C4;L30-40 – see exemplary compounds, specifically "4,4-azobis-(4-cyanovaleric acid)" – also see C3/L58-66)." As further discussed below, this is a factually incorrect assertion. The specified compound is merely named as one of a number of interchangeable free radical initiator chemical reagents and irradiation sources which are used in solution polymerization and disclosed at Col. 4, lines 29-38.

Drumheller is concerned with immobilization of biologically active ligands onto various substrates to produce chemically defined bioactive surfaces. Drumheller, in section 110.4, "Ligand/Polymer Hybrids" states the following:

Hybrid copolymers may be synthesized in which one of the components is the biologically active ligand. These copolymers may then be coated onto a substrate or crosslinked into a three-dimensional network. Since the ligand is a component of the copolymer, no additional ligand immobilization may be necessary to produce bioactive substrates.

Examples are available for particular cases of hybrid copolymers [54, 55, 82–87], including gamma-irradiated crosslinked poly(peptide) [86, 88], dialdehyde crosslinked poly(vinyl alcohol)-glycosaminoglycan [54], poly(amino acid-etherurethane) [47, 87], poly(amino acid-lactic acid) [89], poly(amino acid-carbonate) [90], poly(peptide-styrene) [84], and linear [83] or crosslinked [82] poly(glycoside-acrylamide).

Drumheller does not otherwise disclose free radical initiated polymerization of ethylenically unsaturated monomers to form graft polymers. Other than the above section, Drumheller is concerned with the linking of a biologically active ligands with chemical functional groups on substrates directly or via a bifunctional bridge to form bioconjugates.

Accordingly, it is pointed out that the cited disclosures are not related to the instant stepwise process involving covalently linking a thermally labile radical initiator with the primary or secondary primary amine coupled to a substrate surface nor to the product formed. Accordingly, it is submitted that the rejection should be removed because the cited references are not relevant to the instant invention.

Further, even if combined, the cited references fail to suggest the invention of the instant application; and no prima facie obviousness is demonstrated nor can be maintained.

The instant rejection will be more fully discussed with respect to individual claims.

The Applicants will first discuss product Claim 40 and the corresponding process claim 54 each of which is listed below for the Examiner's convenience.

40. (Previously Presented) A separating material formed by a process comprising the steps of:

a) providing a solid substrate having a substrate surface, wherein primary or secondary amines are coupled to the substrate surface; and

b) forming a graft polymer on the substrate by a process consisting essentially of the reaction steps of:

i) covalently coupling the primary or secondary amines with a thermally labile radical initiator and

ii) contacting the substrate surface with a solution of one or more polymerizable monomers, wherein thermally initiated graft copolymerization of the

monomers forms a structure comprising adjacent functional polymer chains on the substrate surface.

54. (Previously Presented) A method for producing a separating material comprising the steps of:

a) providing a solid substrate having a substrate surface, wherein primary or secondary amines are coupled to the substrate surface; and

b) forming a graft polymer on the substrate by a process consisting essentially of the reaction steps of:

i) covalently coupling the primary or secondary amines with a thermally labile radical initiator and

ii) contacting the substrate surface with a solution of one or more polymerizable monomers, wherein thermally initiated graft copolymerization of the monomers forms a structure comprising adjacent functional polymer chains on the substrate surface.

Horl discloses a 'one-pot' process "for grafting nitrogen-containing polymers, to whose nitrogen atoms substitutable hydrogen atoms are linked, with ethylenically unsaturated monomers in such a manner that the monomers are reacted with the polymers in the presence of a water-containing medium, carbon tetrachloride and of a reducing agent." Col. 4, paragraph beginning at line 25. Pitt "relates to a porous membrane capable of promoting cell attachment and growth and to a process for making the same." Column 1, paragraph beginning at line 14. Specifically, in Pitt, "the coating polymer is directly coated onto the porous substrate without utilization of an intermediate binding chemical moiety. Column 2, beginning at line 45. Drumheller is directed to the immobilization of biologically active (adhesion) ligands to produce chemically defined bioactive surfaces for investigating cell-surface interactions. Title and introductory paragraphs.

It is asserted in the Office Action (pages 4-5) that Horl discloses:

"...

Covalently coupling the amino functional groups with a reducing agent (C8/L1-15, C11/L28-33 – the reducing agent would couple covalently with the amino functional groups due to chemical attraction when exposed in an aqueous or liquid environment with the reducing agent and utilizing a thermal activation,

C11/L43-50 – furthermore see Drumheller on P7 – "Immobilization to Surface Amines" which discusses several compounds to bind chemicals with surface amines – it is considered that the covalent coupling is an inherent intermediate product to produce the final product – the mere fact that the mechanism of Horl is unknown does not further patentability. Further, Drumheller clearly indicates an equivalent mechanism using similar circumstance; albeit more generic to the end product);

Contacting the substrate surface with a solution of polymerizable monomers wherein graft copolymerization of the monomers forms a structure of adjacent functional polymer chains on the substrate surface (C6/L15-60, specifically see also C8/L2-44).

Horl et al. does not disclose the use of a thermally labile radical initiator to promote the polymer grafting process."

For convenience, some of the cited portions of Horl are below (the long listing of unsaturated monomers at lines 15-60 of col. 6 is not included):

8

Graft polymerization can be carried out both in liquid phase, that is, in a melt or solution, and in a solid phase, at which time the base polymer must generally be in a swollen form in order to make possible the access of the monomer to the chains of the base polymer. The swelling can take place either by means of the monomer itself or by means of a further component which does not participate itdelf in the polymerization. The grafting progresses in this instance from the surface to the interior of the polymer. The case can occur thereby that the graft copolymer being produced is soluble in the grafting medium, which accelerates the progress of the grafting because the diffusion paths are not lengthened during the grafting.

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The Reducing Agents

The preferred reducing agent for the application of the process of the invention is sodium dithionite as well as its daughter products such as e.g. rongalite. Other reducing agents such as hydrazine or ascorbic acid, the latter in the alkaline range, can also be used but are less preferred.

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10. Rongalite itself is largely ineffective at room temperature for the process of the invention but is effective at temperatures from 40°–50° C., at which it develops a sufficient redox potential. Rongalite, which is produced industrially as dithionite with formaldehyde, appears to be effective like dithionite itself in a quite similar manner and the addition of complexing Fe ions as well as the elevation of temperature essentially appears to bring about the release of dithionite.

In contrast to the grafting processes on N-halogen polyamides mentioned further above, the grafting speed decreases according to the process of the invention in a certain range with increasing, that is, more negative redox potential. Thus,

8

Graft polymerization can be carried out both in liquid phase, that is, in a melt or solution, and in a solid phase, at which time the base polymer must generally be in a swollen form in order to make possible the access of the monomer to the chains of the base polymer. The swelling can take place either by means of the monomer itself or by means of a further component which does not participate itdelf in the polymerization. The grafting progresses in this instance from the surface to the interior of the polymer. The case can occur thereby that the graft copolymer being produced is soluble in the grafting medium, which accelerates the progress of the grafting because the diffusion paths are not lengthened during the grafting.

Surface Grafting of Form Bodies

The present invention can be used in an especially advantageous manner in the surface grafting of form bodies, especially of tissues, fleeces and membranes of nylon (cf. in this connection DE-OS 39 29 648.2-44). However, other formed parts can also be surface-modified, e.g. for modifying the wetting, sliding and adsorption properties in accordance with the process of the invention.

In a pure surface grafting only the parts of the chains of the base polymer located directly on the surface of the formed body are grafted, so that in those instances in which the graft copolymer being procuded was converted during complete grafting into a graft copolymer soluble in the grafting medium, the non-grafted part of the polymer chain remains in the polymer structure, so that no separating of the graft copolymer from the surface of the form body is possible. Therefore, those monomers can also be used in a pure surface grafting which would result in the case of complete grafting in soluble products. In the case of a matrix grafting of form bodies in which entire chains of the base polymer are grafted, the utility of the monomers is limited to those in the case of which even the graft copolymerizate being produced is insoluble. This can be achieved, if required, by means of a cross-linking grafting under the addition of a multiply ethylenically unsaturated monomer if the monomer provided for an application does not fulfil this precondition itself.

The cited portion of Drumheller is as follows:

Immobilization to Surface Amines

Primary and secondary amine-containing surfaces may be reacted with homo- or heterobifunctional bridges (Fig. 110.7). Amines are more nucleophilic than alcohols, they generally do not require the addition of catalysts, and their addition is faster. These bridges may contain isocyanates [31, 33], isothiocyanates [43], cyclic anhydrides [44], succinimidyl esters [45–47], or epoxides [48, 49].

Isocyanates add to amines with good efficiency but are susceptible to hydrolysis; epoxides and cyclic anhydrides are somewhat less reactive yet are still sensitive to hydrolysis. Hydrolysis-resistant diisothiocyanates have been used for many years to label ligands with reporter molecules; however, the thiourea linkage may be hydrolytically labile (especially at lower pH) and may be unsuitable for investigations of cell-surface interactions. Succinimidyl esters, although not as resistant to hydrolysis as isothiocyanates, have very good reactivity to amines and form stable amide linkages. Hydrolysis is all these reagents is accelerated at higher pH (≥9–10).

Coupling to surface-bound amines is performed in organic conditions (DMF, DMSO, acetone) for 1–3 hr. Coupling of amine-bearing ligands onto immobilized bridges is performed in buffered media, pH 8–10.5, 2–12, 1–10 mg/ml. Excess reagent can be displaced with buffered solutions of tris(hydroxymethyl)aminomethane, aminoethanol, glycine, or mercaptoethanol, or hydrolysis.

Bifunctional aldehydes, such as glutaraldehyde and formaldehyde, have been used classically as crosslinkers for purposes of immunohistochemistry and ultrastructural investigations. They have been used also to couple ligands onto amine-bearing substrates [50–52]. Hydrolysis of aldehydes is usually not a concern, since the hydrolysis product, alkyl hydrate, is reversible back to the carbonyl. Amines add to aldehydes to produce imine linkages over a wide range of pH (6–10). These Schiff bases are potentially hydrolytically labile; reductive amination can be performed with mild reducing agents such as sodium

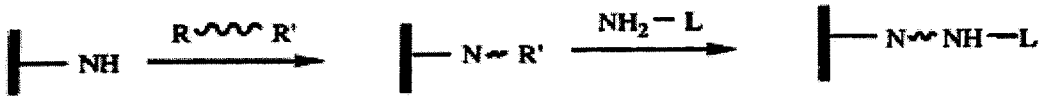

FIGURE 110.7 Primary and secondary amine-containing surfaces may be reacted with homo- or heterobifunctional bridges.

cyanoborohydride, pH 8–9, without substantial losses in ligand bioactivity [53]. Acetalization of polyhydric alcohols may commence in the presence of Lewis acid catalysts followed by dehydrating the hemiacetal linkage, an acetal [54, 55]. The dehydration conditions (air-drying followed by 70–90°C, 2 hr) may damage many biologic ligands.

Alkyl halide-bearing surfaces can be coupled to amine-bearing ligands [49, 56, 57]; their reaction is slower, but they are resistant to hydrolysis. Ligands can be immobilized in buffered medium (pH 9–10), 12–24 hr, 1–10 mg/ml, or in organic medium. Heat may be used to increase yields (60–80°C).

The statement in the Office Action that the reducing agent of Horl would couple covalently with the amino functional groups to provide an inherent intermediate product to produce the final product in no way provides a chemically cognizable intermediate product corresponding to the product of step i) of claim 40 or claim 54 of the instant application, and the disclosure of Drumheller does not remedy this shortcoming. A significant difference of the process as claimed to what is disclosed in Horl is the fact that in the claimed process steps i) and ii) are separate steps which happen in sequence and not at the same time. Horl does not apply several separate steps, but makes use of a "one-pot reaction". In other words, the reaction

described by Horl is a polymerization reaction which starts not on the surface of the substrate as in the presently claimed process, but in solution. Coupling by radicals with the substrate will occur, in the process following Horl, unguided and on a random basis and statistically just as often as between, for example, the monomers present in the solution. The potential Horl process products would thus show a higher degree of cross-linked portions and irregular coupling of polymerized monomers. As pointed out in the third paragraph at page 3 of the description of the instant application:

> Another advantage of the present invention lies in the covalently coupling of the radical initiator to the amino-functional groups on the solid substrate. Thereby, the occurrence of homopolymerization in the reaction solution is avoided or at least minimized. The radical initiator, which is bound to the solid substrate, forms radicals upon temperature increase, and part of the radical initiator structure becomes part of the polymer chains, which are formed from the solid substrate surface. The polymer chains of the present invention develop from the surface of the substrate without the formation of undesired cross-linkages between the chains, thus the process of the present invention is considered to provide a very "clean" chemistry.

Thus, the product of claim 40 or the method of claim 54 contains polymer chains containing a portion of the radical initiator, a circumstance not demonstrated in Horl, nor suggested by Drumheller. In addition, the instant process avoids the random coupling of monomers to a resin found in Horl. In the present invention, the polymer develops from a defined starting point, i.e. the amino group located on the resin. The precursor to the active radical is formed, in a first step, upon chemical bonding of the thermolabile initiator to the amino group. Only when the monomers are added in a second step will they be coupled to the activated site created by thermolysis of the initiator.

As to Pitt, is asserted in the Office Action (page 5) that Pitt discloses:

"...

Covalently coupling a thermally labile radical initiator to the membrane (C4/L30-40 – see exemplary compounds, specifically "4,4'-azobis-(4-cyanovaleric acid)" – also see C3/L58-66)

Contacting the substrate surface with a polymerizable monomer solution (C4/L12-28 – see exemplary monomers, see also C3/L58-67)."

For convenience, the cited portions of Pitt are below:

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Suitable initiators and cross-linking agents for the monomers set forth above are well known in the art. For example, when utilizing acrylates as the polymerizable monomer, suitable chemical polymerization initiators include ammonium persulfate, potassium persulfate, 4,4-azobis-(4- cyanovaleric acid), 2,2-azobis (2-amidinopropane) hydrochloride, potassium hydrogen persulfate or the like. In addition to chemical initiation, ultraviolet light, electron beam or cobalt-60 irradiation can be used to initiate polymerization. When utilizing acrylates of methacrylates or methacrylamides as the polymerizable monomer, suitable cross-linking agents

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Subsequent to wetting the porous membrane, a reagent bath comprising the cell adhesion and growth promoting composition, a free radical polymerizable monomer, a polymerization initiator and cross-linking agent in solvent comprising water or water and a water miscible, polar, organic solvent for these constituents is contacted with the porous membrane under conditions to effect free radical polymerization of the monomer and coating on the porous membrane with a cross-linked polymer. When utilizing a multifunctional cross-

4

Any monomer for coating the membrane can be utilized herein so long as it is capable of being polymerized by free radical polymerization, can be cross-linked and does not destroy the biological functionality of the cell attachment and/or growth promoting substances utilized. Representative suitable polymerizable monomers include hydroxyalkyl acrylates or methacrylates including 1-hydroxyprop-2-yl acrylate and 2-hydroxyprop-1-yl acrylate, hydroxypropyl methacrylate, 2,3-dihydroxypropyl acrylate, hydroxyethyl acrylate, hydroxyethyl methacrylate or the like or mixtures thereof. Other polymerizable monomers which can be utilized herein include acrylic acid, 2-N,N-dimethylaminoethyl methacrylate, sulfoethyl methacrylate or the like, acrylamides, methacrylamides, ethacrylamides, etc. These monomers are examples of polar-substituted or functionally substituted monomers useful herein.

The statement in the Office Action that Pitt discloses covalently coupling a thermally labile radical initiator to the membrane prior to polymerization mischaracterizes the disclosure. Pitt only discloses and enables polymerization of solutions containing polymerizable monomers and polymerization initiators to form a coating; there is absolutely no disclosure of the carboxylic acid function of 4,4'-azobis-(4-cyanovaleric acid) forming a covalent bond with the membrane prior its thermal decomposition to provide a radical to initiate polymerization. Certainly, Pitt does not relate to "a structure comprising adjacent functional polymer chains on the substrate surface."

The Applicants will next discuss the process claim 80 which is listed below for the Examiner's convenience.

80. (Previously Presented) A method for producing a separating material comprising the step of:

contacting the substrate surface of a solid substrate having a substrate surface, wherein primary or secondary amines are coupled to the substrate surface and a thermally labile radical initiator is covalently coupled to the primary or secondary amines,

with a solution of one or more polymerizable monomers, wherein thermally initiated graft copolymerization of the monomers forms a structure including adjacent functional polymer chains on the substrate surface.

The process of claim 80 requires an isolated "solid substrate having a substrate surface, wherein primary or secondary amines are coupled to the substrate surface and a thermally labile radical initiator is covalently coupled to the primary or secondary amines" as a starting material for the process to form "a structure comprising adjacent functional polymer chains on the substrate surface." As is clear from the discussion above, there is no disclosure nor suggestion of such a starting material in any of the cited references, or combinations thereof.

As to claim 41, it is stated at page 6 of the Office Action:

> Specifically regarding claims 40-41, Applicant is noted that the claim is a product-by-process type claim. Accordingly, it is asserted that the wash step of claim 41 does not further limit the structure or provide an unexpectedly different structure. Accordingly, Applicant must either further define the product or provide evidence of its difference from that of the prior art. Regarding the method limitations recited in claim(s) 40-41, the examiner notes that even though a product-by-process is defined by the process steps by which the product is made, determination of patentability is based on the product itself. In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985). As the

Claim 41 is listed below for the Examiner's convenience.

> **41. (Previously Presented) The separating material of claim 40, wherein the step of covalently coupling the primary or secondary amines with a thermally labile radical initiator is followed by at least one washing or rinsing step prior to contacting the substrate surface with a solution of one or more polymerizable monomers.**

Claim 41 accentuates the fact that the process and the resulting product of the instant claims are inherently different from anything disclosed or taught by the cited references. It is impossible for the cited one-pot radical polymerization processes to provide an isolatable intermediate material in which the amines of the material are covalently coupled with a thermally labile radical initiator, the covalently coupled residue of which will form a radical upon which the polymer chain will grow upon thermolysis in the subsequent step.

Because none of the cited conditions is true for the subject matter of claim 40, claim 54 or claim 80, nor claims which depend from any of them, and no combination of the cited references suggests the subject matter of the instant claims as to the processes described or the products formed by the processes, it is submitted that there is no prima facie obviousness under 35 U.S.C. § 103(a) over the combination of references at point 8. If it is considered that prima facie obviousness was provided, it is submitted that the obviousness is rebutted. Accordingly, it is requested that this rejection be removed.

Claim Rejections Under 35 U.S.C. § 103

At point 9 of the Office Action, claims 67-70, 72, 76, and 83 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,556,708 to Horl et al. (hereinafter "Horl") in view of U.S. Patent No. 5,037,656 to Pitt et al. (hereinafter "Pitt") and further in view of U.S. Patent No. 6,774,102 to Bell et al. (hereinafter "Bell").

Claims 67-70 involve a method or a material using or containing the separating material of claim 40, claim 76 involves a method dependent on a claim dependent on method claim 54, and claim 83 involves a method dependent on a claim dependent on method claim 80.

Bell discloses immobilizing onto a solid state medium polydisperse oligopeptides of amino acids which are positively charged at physiological pH of 7.2 for adsorbing endotoxins. See, e.g. the summary of the invention beginning at col. 3, line 24. Bell does not disclose processes for the syntheses of a solid state medium.

In the first place, a person of skill in the art, using Bell as a starting point, would not consider Horl for further guidance. Horl is not concerned with and does not refer in any way to the removal of endotoxins from blood. It is important for any such material which will be used for the treatment of blood of a person in needs to fulfill certain requirements, such as biocompatibility, blood-compatibility, and non-toxicity. The necessity of using the toxic carbon tetrachloride in the process of Horl would exclude Horl from consideration.

Accordingly, it is submitted that the rejection should be removed because the cited references are not relevant to the instant invention.

Even if Horl or Horl and Pitt are considered with Bell, the references would not provide the presently claimed process.

The basis for the instant rejection requires that the separating material of claim 40, the method of claim 54, or the method of claim 80 be obvious in view of Horl and Pitt. As discussed above, these claims are not obvious in view of Horl and Pitt. Accordingly, applying the teaching of Bell to provided the subject matter of claims 67-70, 72, 76, and 83 is moot.

Accordingly, because none of the cited conditions is true for the subject matter of claim 40, claim 54 or claim 80, nor claims which depend from any of them or incorporate their definitions, and no combination of the cited references suggests the subject matter of the instant claims as to the processes described or the products formed by the processes, it is submitted that there is no prima facie obviousness under 35 U.S.C. § 103(a) over the combination of references at point 9. If it is considered that prima facie obviousness was provided, it is submitted that the obviousness is rebutted. Accordingly, it is requested that this rejection be removed.

Claim Rejections Under 35 U.S.C. § 103

At point 10 of the Office Action, claim 71 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,556,708 to Horl et al. (hereinafter "Horl") in view of U.S. Patent No. 5,037,656 to Pitt et al. (hereinafter "Pitt") and further in view of U.S. Patent No. 4,668,399 to Duggins (hereinafter "Duggins").

Duggins discloses a hollow fiber plasmapheresis module and process for separating plasma from blood.

In the first place, a person of skill in the art, using Duggins as a starting point, would not consider Horl for further guidance. Horl is not concerned with and does not refer in any way to separating plasma from blood. It is important for any such material which will be used for the treatment of blood of a person in needs to fulfill certain requirements, such as biocompatibility, blood-compatibility, and non-toxicity. The necessity of using the toxic carbon tetrachloride in the process of Horl would exclude Horl from consideration.

Accordingly, it is submitted that the rejection should be removed because the cited references are not relevant to the instant invention.

Even if Horl or Horl and Pitt are considered with Duggins, the references would not provide the presently claimed process.

Claim 71 incorporates the separating material of claim 40. The basis for the instant rejection requires that the separating material of claim 40 be obvious in view of Horl and

Pitt. As discussed above, these claims are not obvious in view of Horl and Pitt. Accordingly, applying the teaching of Duggins to provided the subject matter of claim 71 is moot.

Accordingly, because none of the cited conditions is true for the subject matter of claim 40, nor claims which incorporate the definitions of claim 40, and no combination of the cited references suggests the subject matter of the instant claim as to the product formed by the process disclosed in claim 40, it is submitted that there is no prima facie obviousness under 35 U.S.C. § 103(a) over the combination of references at point 10. If it is considered that prima facie obviousness was provided, it is submitted that the obviousness is rebutted. Accordingly, it is requested that this rejection be removed.

Claim Rejections Under 35 U.S.C. § 103

At point 11 of the Office Action, claims 73-75, 77-79, and 86-88 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,556,708 to Horl et al. (hereinafter "Horl") in view of U.S. Patent No. 5,037,656 to Pitt et al. (hereinafter "Pitt") and further in view of U.S. Patent No. 4,618,533 to Steuck (hereinafter "Steuck").

As a first point, it is noted that Steuck, as well as Horl and Pitt, is directed to a "one-pot" process. The process of Steuck is for coating a porous membrane with a polymerized, cross-linked monomer as a direct coating to provide a porous membrane having bulk properties which differ from its surface properties and the resulting product. In relation to Horl and Pitt, as discussed above, Steuck adds nothing which would cause one to consider it as to the rejected claims; and, accordingly, the combination is not relevant.

Even if the combination is considered, it is submitted that a prima facie case of obviousness has not been made.

Claims 73-75 are product claims depending from claim 40; claims 77-79 are process claims depending from claim 54; and claims 86-88 are process claims depending from claim 80. As discussed above Horl and Pitt do not teach or suggest these claims. Steuck adds no more. As described at col.3, lines 36-45, it is a one-pot process; and there is no element relating to the covalently linked radical initiator of the instant application:

> **Subsequent to wetting the porous membrane, a reagent bath comprising a free radical polymerizable monomer, a polymerization initiator and cross-linking agent in a solvent for these three constituents is contacted with the porous membrane under conditions to effect free radical polymerization of the monomer and coating of the porous membrane with the cross-linked polymer. When the monomer is difunctional or has higher functionality, an additional cross-linking agent need not be utilized.**

Accordingly, because none of the cited conditions is true for the subject matter of claim 40, claim 54 or claim 80, nor claims which depend from any of them or incorporate their definitions, and no combination of the cited references suggests the subject matter of the instant claims as to the processes described or the products formed by the processes, it is submitted that there is no prima facie obviousness under 35 U.S.C. § 103(a) over the combination of references at point 11. If it is considered that prima facie obviousness was provided, it is submitted that the obviousness is rebutted. Accordingly, it is requested that this rejection be removed.

At point 12 of the Office Action, the following is asserted:

> Applicant alleges non-obviousness in light of the failure of both references to provide enumerated examples that may be explicitly and directly linked to the instant claimed (e.g. Horl and Pitt fail to discuss an example using primary amino groups).
>
> This is not persuasive. The lack of examples does not prove non-obviousness. A reference is taken for all that it teaches.

Applicants traverse the conclusions drawn in the instant circumstances. One of skill in the art seeking a teaching as to preparing a material with specified polymeric chains specifically attached to primary or secondary amino groups would find no effective teaching from a reference (Horl) which only describes a grafting reaction (presumably) to the amide nitrogen of nylon resins and emphasizes the use for polyamides and polyurethanes. See, for example Horl at col. 12, lines 29-34:

> chain. The N-substituted derivatives of the base polymer
> 30 produced thus represent totally new classes of polymers in the case of polyamides and urethanes since they no longer exhibit the typical peptide or carbamic acid group but rather secondary amide groups or N-substituted carbamic acid groups in the main chain. As a consequence of the lack of a

Merely mentioning "polymers having primary or secondary amino groups in a side chain" is not a scientific teaching for one of skill in the art; indeed, it is only speculation.

Similarly, one of skill in the art would find no teaching in Pitt, which only discloses "free radical polymerization of the monomer and coating on the porous membrane with a cross-linked polymer." Col. 3, lines 65-67. There is no disclosure of an amine bearing primary or secondary amino groups. The examples of Pitt are limited to coating microporous polytetrafluoroethylene. For one of skill in the art, from the disclosure of Pitt, graft polymerization, can only be envisioned by generating radicals on the substrate chain, using strong oxidizing agents or high-energy radiation. (See above.) Pitt mentions electron beam or cobalt-60 irradiation for radical initiation. Col. 4, lines 36-38.

At point 12 of the Office Action, the following is asserted:

> Horl is silent as to the specific reaction mechanism. However, See Drumheller for evidence at P7. Horl performs reaction using rongalite which is related to formaldehyde as discussed in Drumheller. Horl is in fact performing a reductive amination which is considered equivalent and or interchangeable in this instance with a thermally labile radical initation process. Additionally, the Horl reference and the Pitt references would both inherently form intermediary products along the way to forming the final material. If Applicant disagrees with an argument of inherency, Applicant should submit evidence, made of record, showing that the intermediate would not inherently occur.

Applicants emphatically disagree with the above argument of inherency. As discussed below, rongalite as used Horl bears no relation to formaldehyde as disclosed in Drumheller. Further Horl is <u>not</u> performing a reductive amination as discussed in Drumheller. The reaction known as reductive amination is entirely different from the free radical polymerization reaction of Horl.

As is demonstrated in Exhibits 1A-1D, reductive amination, also known as reductive alkylation, is a process by which an aldehyde or ketone is used to alkylate ammonia, a primary amine or a secondary amine. When formaldehyde is used in this reaction, the formaldehyde is not a reducing agent, but rather the alkylating agent which forms an N-methyl group upon the reduction of the intermediate imine, enamine or iminium species.

In the section "Immobilization to Surface Amines" in the paragraph beginning at the bottom of page 7 (also a part of Drumheller provided above) discloses the following:

> Bifunctional aldehydes, such as glutaraldehyde and formaldehyde, have been used classically as crosslinkers for purposes of immunohistochemistry and ultrastructural investigations. They have been used also to couple ligands onto amine-bearing substrates [50–52]. Hydrolysis of aldehydes is usually not a concern, since the hydrolysis product, alkyl hydrate, is reversible back to the carbonyl. Amines add to aldehydes to produce imine linkages over a wide range of pH (6–10). These Schiff bases are potentially hydrolytically labile; reductive amination can be performed with mild reducing agents such as sodium cyanoborohydride, pH 8–9, without substantial losses in ligand bioactivity [53]. Acetalization of poly-

As illustrated in Exhibits 2A-2B, formaldehyde does not act as a reducing agent in these reactions, but reversibly forms a methylene (-CH_2-) bridge between two heteroatoms with the loss of water. See Fig. 2 of Exhibit 2A and Figure 6 of Exhibit 2B. Glutaraldehyde forms imines (Schiff bases) with amino groups of proteins. See Fig. 4 of Exhibit 2A and Figure 12 of Exhibit 2B. Drumheller notes that these imines (Schiff bases) can be reduced with mild reducing agents such as sodium cyanoborohydride to effect reductive amination, as discussed above and in Exhibits 1A-1D. This chemistry is further demonstrated in the references cited in Drumheller.

Thus, reference 51, Yamagata, et al. (Exhibit 3A), at page 8013, second column, under "*Cell Adhesion Assay*" discloses cross-linking (fixing) with formaldehyde:

> **well, and the plates were incubated for 2 h at 37 °C. After unattached cells were removed by two washes with Hanks' balanced salt solution, attached cells were fixed in 2% (w/v) formaldehyde in phosphate-buffered saline at 4 °C for 10 min and then stained with 1% (w/v) toluidine blue/3% (w/v) formaldehyde in phosphate-buffered saline.**

and the section beginning at the bottom of the column discloses cross-linking with glutaraldehyde:

> *Preparation of GRGDS-derivatized Serum Albumin*—The fibronectin cell-binding sequence GRGDS was cross-linked to bovine serum albumin (molar ration of peptide to serum albumin = 50:1) by a modification of the glutaraldehyde-promoted Schiff's base-forming reaction of Patel and Lodish (44). Briefly, 5 mg of the peptide and 11.5 mg of bovine serum albumin were dissolved in 1 ml of 0.1 M sodium phosphate, pH 7.5, and to this solution was added dropwise 0.5 ml of 20 mM glutaraldehyde aqueous solution with stirring at 20 °C. The mixture was left for a further 30 min at 20 °C and then the remaining aldehyde groups were blocked with 0.1 M glycine, pH 7.0. The resulting GRGDS-derivatized serum albumin was isolated by chromatography on Sephadex G-100.

Reference 50 of Drumheller, Werb, et al. (Exhibit 3B) discloses cross-linking with glutaraldehyde to the amino groups of a modified glass surface beginning at the bottom of page 878, second column:

> ***Covalent Protein Coating of Glass Coverslips for Specific Adhesion***
>
> For covalently linked Fn, type I collagen, peptides containing the arg-gly-asp (RGD) cell recognition sequence, or purified anti-FnR IgG or Fab, polypeptides were conjugated to glass coverslips as follows. Coverslips were washed sequentially with 20% concentrated H_2SO_4, water, 0.1 N NaOH, and water. Dried coverslips were exposed to γ-aminopropyltriethoxysilane (Sigma Chemical Co.) for 4 min at ambient temperature, followed by water and PBS rinses. The coverslips were incubated with 0.25% glutaraldehyde in PBS for 30 min at 22°C, washed several times with PBS, and covered with ECM proteins or antibody solutions (20–700 μg/ml) for 1 h at ambient temperature, washed with PBS, and used immediately. All steps after the glutaraldehyde treatment were done with sterile reagents and utensils. Freshly trypsinized cells resuspended in DME-LH were plated on the glass coverslips containing immobilized proteins in 24-well plates.

Reference 52 of Drumheller, Robinson, et al. (Exhibit 3C) similarly discloses cross-linking with glutaraldehyde to the amino groups of a modified glass surface beginning at the bottom of page 659:

> Aminoalkylsilane glass (2 g) was stirred in a cold 1% aqueous solution of

glutaraldehyde for 30 min. The derivative was rinsed with water and suspended in 10 ml of 0.05 M phosphate buffer, pH 7.5, containing 40 mg of α-chymotrypsin (EC 3.4.4.5) (Miles–Seravac (PTY) Ltd., U.K.). After 2 h at 4°C the beads were washed thoroughly with 1 M NaCl until no further activity was detectable in the washings. The immobilised chymotrypsin was assayed using *N*-acetyl-L-tyrosine ethyl ester as described by Kay and Lilly[3]. The immobilised preparation contained 16 mg of chymotrypsin/g support. When

Also, at point 12 it is stated:

> The argument that Horl doesn't explicitly disclose grafting onto primary amino groups is not persuasive. Horl inherently when using the primary amino substrate would have this happen.

In addition to the discussion provided above, this statement overlooks the scientific facts provided by declaration on July 28, 2010, showing the failure of the Horl process to function on a resin bearing primary amino groups in which the process of the instant application proceeds and makes a product which successfully adsorbs BSA.

Also, at point 12 it is stated:

> Further arguments to the lack of mechanistic explanation in Horl are considered moot in view of the above discussion and the Drumheller evidence.
>
> Arguments regarding the presence or non-presence of CCl4 are not commensurate with the scope of the instant claims.
>
> With regards to Pitt, the mechanism would inherently result in covalent coupling followed by graft copolymerization. Additionally, using the starting material of Horl would further provide for this inherent occurrence.
>
> Pitt's absence of disclosure of intermediate binding moiety does not provide for non-obviousness. The reactants of Pitt would inherently absent **evidence** provide for an intermediary reaction product which would then form the final graft copolymer.

As discussed in detail above, Applicants traverse these conclusions. As to Pitt, there is absolutely no evidence of a covalent bond forming between a radical initiator and a substrate prior to polymerization. The teaching is limited to a radical formed in solution which initiates polymerization and cross-linking.

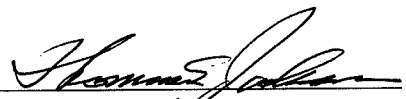
In view of the forgoing, it is submitted that this application is in condition for allowance. Allowance is respectfully requested. If the Examiner believes that a telephonic

interview would expedite the allowance of this application, the Examiner is requested to contact the undersigned for prompt resolution of any outstanding issues.

It is respectfully requested that, if necessary to effect a timely response, this paper be considered as a Petition for an Extension of Time sufficient to effect a timely response and that the requisite fees be charged, or any overpayment in fees credited, to the Account of Barnes & Thornburg, Deposit Account No. 10-0435 with reference to file 52759-215213.

Respectfully submitted,

BARNES & THORNBURG LLP



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Enclosures: Exhibits 1A-1D, 2A-2B, 3A-3C